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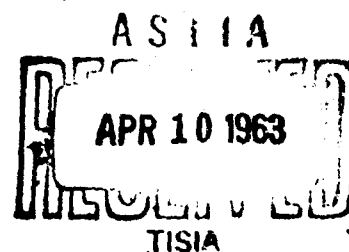
THE USE OF STREPTOMYCIN IN THE PREVENTION OF
ACUTE RADIATION SICKNESS

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- USSR -

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THE USE OF STREPTOMYCIN IN THE PREVENTION OF
ACUTE RADIATION SICKNESS

[Following is a translation of an article by L.F. Semenov, in Antibiotiki (Antibiotics), Vol VII, No 10, Moscow, 1962, pp 912-196.]

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The reports which have appeared in recent years attest to the fact that certain antibiotics may have a protective effect upon their prophylactic use prior to exposure to ionizing radiation in lethal doses [1-3].

A suggestion has been advanced that the protective effect of antibiotics under these conditions is not connected with their antibacterial action but is caused by their intervention as chemical agents during the initial changes which had been induced in tissues by means of radiation [4,5]. In this connection, of special interest is the testing of antibiotics by means of their single administration within 5-30 minutes prior to irradiation, during the period when antiradiation properties of the usual chemical protectors are most clearly manifested. In our previous investigation [6] we indicated that, under these conditions (five minutes prior to irradiation of mice with an LD₁₀₀ X-ray dose), antibiotics of the penicillin group proved to be ineffective, whereas protamin-sulfate (ecmolin) exerted a protective effect and increased the effect of other antiradiation preparations.

In the present work we conducted an investigation of streptomycin and its analogues (dihydrostreptomycin and a combination of streptomycin and penicillin) submitted by Z.V. Yermol'yeva, upon their isolated use and in combination with certain protective agents in acute radiation sickness of animals.

Experiments were carried out on 2,738 white mice (male and female) weighing 18-22 grams. The radiation sickness was produced by means of a single total irradiation with gamma-rays of radioactive cobalt in a dose of 1050-1100 r LD₁₀₀. The animals were irradiated on an experimental cobalt irradiator with a 400c charge, dose strength of 85-110 r/min in the air, in the center of the chamber. We recorded the death periods, the survival rate of the animals, and examined the condition of cells of the peripheral blood.

Antibiotics were injected subcutaneously in the form of aqueous solutions in a 0.2-0.4 ml volume of fluid, in the basic part of the experiments -- within 5 to 10 minutes prior to irradiation.

In some series the antibiotics were given for comparison purposes within 24 hours prior to, or repeatedly, thrice, within 24-72 hours after, irradiation.

As standard antiradiation preparations, employed for the purpose of comparison or for combining with antibiotics, we selected beta-mercaptoethylamine (in a 150 mg/kg dose), and the combination of adrenalin (0.6-1 mg/kg) with acetylcholine (40-50 mg/kg) which, under our conditions, produced survival of 20-30% of mice, while all control animals perished.

In the first series of experiments (370 mice) we tested the effect of antibiotics of the streptomycin group following their isolated single use prior to irradiation. Under these conditions, streptomycin, dihydrostreptomycin, and combiotique (combination of penicillin with streptomycin in a 1:1 ratio) had no effect whatever on the course of radiation sickness. The results of experiments are shown in Table 1.

In the second series of tests (1,072 animals) we employed streptomycin combined with antiradiation agents, in order to increase their protective effect. The conducted experiments showed that streptomycin, administered simultaneously with beta-mercaptoethylamine and in combination with adrenalin and acetylcholine, not only fails to increase their antiradiation effect, but even weakens it. Thus, for instance, when combined with beta-mercaptoethylamine, it reduces the survival rate from 17.5 to 11, and upon addition to adrenalin and acetylcholine, it reduces the survival rate from 20 to 13% (Table 2).

Table 1

① Антибиотик	② Доза препарата (в мг)	③ Время введения препарата	④ Число животных	⑤ Выжило к 30-му дню	⑥ % выживших
⑦ Стрептомицин	2-5	5 минут до облучения	121	1	0,8
⑧ Дигидрострептомицин	2-10	То же	50	0	0
⑨ Комбиотик	2-10	" "	59	0	0
⑩ Контроль	—	—	140	0	0

1. Antibiotic; 2. Preparation dose per mouse (in mg); 3. Time of injection of the preparation; 4. Number of animals; 5. Survived toward the 30th day; 6. Percentage of survived animals; 7. Streptomycin; 8. Dihydrostreptomycin; 9. Combiotique; 10. Control; 11. Five minutes prior to irradiation.

Table 2
Effect of Prophylactic Administration of Streptomycin on the Protective Action of Antiradiation Agents (Gamma-Irradiation with 1100 r)

① Препарат	② Доза препарата (в мг)	③ Время введения препарата	④ Число животных	⑤ Выжило к 30-му дню	⑥ % выживших
⑦ Бетамеркаптоэтиламин	3	5 минут до облучения	240	42	17,5
⑧ Стрептомицин + бетамеркаптоэтиламин	2 3	То же	240	26	11
⑨ Адреналин + ацетилхолин	12,5γ 0,5	" "	136	29	20
⑩ Стрептомицин + адреналин + ацетилхолин	2 12,5γ 1,5	" "	136	18	13
⑪ Контроль	—	—	320	0	0

1. Preparation; 2. Preparation dose per mouse (in mg); 3. Time of injection of the preparation; 4. Number of animals; 5. Survived on the 30th day; 6. Percentage of survived animals; 7. Beta-mercaptoethylamine; 8. Streptomycin + beta-mercaptoethylamine; 9. Adrenalin + acetylcholine; 10. Streptomycin + adrenalin + acetylcholine; 11. Control; 12. Five minutes prior to irradiation.

The detected negative effect of streptomycin on the protective action of antiradiation agents should be taken into account in preparation of the protective "prophylactic mixtures." Obviously, one should not combine streptomycin with sulfur-containing or amino-containing agents. At the same time, many investigators proved convincingly that streptomycin represents a valuable means for the treatment of radiation sickness [7-13]. It has been established that its early use -- during the first days of the disease -- is expedient for the successful effect on the infection phase. In this connection, the question arises of the compatibility of the prophylaxis of radiation sickness with the therapeutic use of streptomycin, and of the time interval during which such combination is possible.

In order to settle this question we conducted a series of experiments (310 mice) on the testing of the combination of beta-mercaptoethylamine, used prophylactically, with streptomycin which had been repeatedly injected subcutaneously following irradiation.

The results of the experiments (Table 3) attest to the fact that the therapeutic use of streptomycin, starting within 24 hours following irradiation, did not hamper the realization of the protective effect of beta-mercaptoethylamine.

Under given experimental conditions, in the grave form of radiation sickness (LD_{100}), a single therapeutic administration of streptomycin did not lead to the survival of irradiated animals. However, when combined with prophylaxis, the additional streptomycin therapy somewhat intensifies the beneficial effect of the protective agent and increases the survival rate of mice.

Comparison of obtained data with the few available works on the prophylactic use of streptomycin [14,15] points to a certain discrepancy in the results. Whereas in these reports a positive effect of streptomycin had been established, in our experiments the prophylactic administration of streptomycin proved to be ineffective and, when combined with other protective agents, it even weakened their effect.

In addition to differences in the object of observation (ascitic cells, leucocytes, or rats) and radiation doses (a higher dose in this work), special attention should be given to the duration of the prophylactic use of streptomycin. In the published reports streptomycin was used repeatedly or at a single dose, but its administration was terminated within 24 hours prior to the use of radiation. In the present work, we studied the effect of streptomycin injected only directly before irradiation (within 5 minutes).

Table 3

Combination of Prophylaxis by Means of Beta-Mercaptoethylamine
With the Therapeutic Use of Streptomycin (1050 r Gamma-
Irradiation)

① Препарат	② Доза препара- та на мышь (в мг)	③ Время введения препарата	④ Число жи- вых	⑤ Число к исходу к 30-му дню	⑥ % выживших
⑦ Бетамеркаптоэтил- амин	3	⑪ 5 минут до об- лучения	90	27	30
⑧ Бетамеркаптоэтил- амин + стрепто- мицин (повторно)	3 2	⑫ 24, 48, 72 часа после облуче- ния	90	32	35
⑨ Стрептомицин	2	⑫ То же	20	0	0
⑩ Контроль	—	—	110	0	0

- | | |
|---|--|
| 1. Preparation; | 7. Beta-mercaptoethylamine; |
| 2. Preparation dose per mouse
(in mg); | 8. Beta-mercaptoethylamine +
streptomycin (repeatedly); |
| 3. Time of injection of the
preparation; | 9. Streptomycin |
| 4. Number of animals; | 10. Control; |
| 5. Survived on the 30th day; | 11. Five minutes prior to
irradiation; |
| 6. Percentage of survived
animals; | 12. 24, 48, 73 hours follow-
ing irradiation. |

In order to verify our assumption in regard to the importance of the periods of prophylactic administration of streptomycin, we carried out special tests by combining streptomycin, injected within 24 hours prior to irradiation, with protective agents employed directly before irradiation. In these tests (180 mice) the combination of streptomycin (24 hours prior to irradiation) and beta-mercaptoethylamine (five minutes prior to irradiation) produced a somewhat better effect (31% of survivals), than beta-mercaptoethylamine only (23% of survivals). Thus, the negative effect of streptomycin is apparently manifested only under conditions of its use immediately prior to irradiation. The effect of possible weakening of the action of antiradiation agents by streptomycin should be taken into consideration in clinical practice. The inclusion of streptomycin in the complex prophylactic prescriptions simultaneously with different protective substances is obviously undesirable. As regards the

mechanism of the unfavorable effect of streptomycin on the protective action of antiradiation agents, it is probably based on the physiological antagonism between streptomycin on the one hand, and the sulfur-containing agents and certain amines, on the other. Thus, for instance, it has been established by investigators [16,17] that beta-mercaptoethylamine prevented toxic-degenerative changes in the nervous cells of rabbits following dihydrostreptomycin poisoning. The same preparation protected mice from acute streptomycin poisoning. These observations found confirmation in our supplementary experiments (tests on 120 mice).

Streptomycin intoxication abated following the preliminary use of beta-mercaptoethylamine, or combination of adrenalin with acetylcholine. Subsequent tests showed that the protective effect in this combination against the toxic effect of streptomycin depends on adrenalin. A different staging of the experiments (tests on 466 mice), namely the use of small streptomycin doses and toxic doses of sulfur-containing agents, or adrenalin, also confirmed their antagonism. In these tests, streptomycin protected against intoxication with beta-mercaptoethylamine and adrenalin. Fig. 1 shows the results of a preliminary use of streptomycin following intoxication of animals with adrenalin. At doses of 0.2-0.4 mg of adrenalin, streptomycin increases twice as much the survival rate of poisoned animals. In a separate series of experiments, it has been established that streptomycin reduces the toxic pulmonary edema which develops following the administration of large doses of adrenalin (observations on 220 animals) (Fig. 2). Thus, the unquestionable presence of antagonistic effects of streptomycin and antiradiation agents, observed in these experiments, probably determines its negative effect under conditions of the prophylaxis of radiation sickness.

Conclusions

1. A single prophylactic administration of streptomycin, dihydrostreptomycin, and a mixture of streptomycin with penicillin, immediately prior to irradiation exerts no protective effect.
2. Simultaneous combination in the prophylaxis of radiation sickness of sulfur-containing or amino-containing agents with streptomycin reduces their protective antiradiation effect.
3. Therapeutic administration of streptomycin, starting on the 2nd day following irradiation exerts a positive effect and increases the effect of prophylactic protective agents.

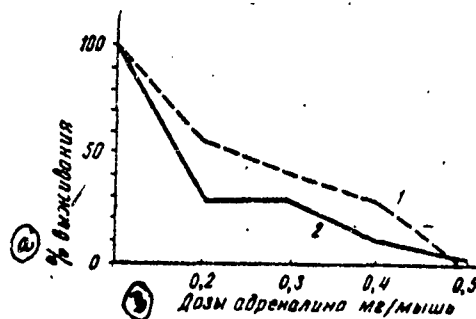


Fig. 1. Effect of streptomycin on adrenalin poisoning (survival rate of mice).

1 - adrenalin; 2 - streptomycin + adrenalin.

a - survival ratio; b - adrenalin doses in mg/mouse.

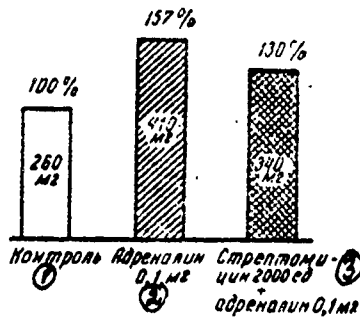


Fig. 2. Effect of streptomycin on the development of adrenalin edema of the lungs in mice (weight changes within an hour, following administration of the preparation).

1 - control; 2 - adrenalin, 0.1 mg; 3 - streptomycin 2000 units + adrenalin 0.1 mg.

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